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ORIGINAL RESEARCH

Quantitative Echocardiographic Determinants of Clinical Outcome in Asymptomatic Patients With Aortic Regurgitation

A Prospective Study

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OBJECTIVES The purpose of this study was to define the link between aortic regurgitation (AR) quantitation and clinical outcome in asymptomatic patients with AR.

BACKGROUND Quantitative American Society of Echocardiography (QASE) thresholds are recommended for AR assessment, but impact on clinical outcome is unknown.

METHODS We prospectively enrolled (1991 to 2003) 251 asymptomatic patients (age 60 $\pm$ 17 years) with isolated AR and ejection fraction $\geq$50% with quantified AR and left ventricular (LV) volumes using Doppler-echocardiography.

RESULTS Survival under medical management was independently determined by baseline regurgitant volume (RVol) (adjusted hazard ratio [HR] 1.22 [95% confidence interval (CI) 1.08 to 1.35] per 10 ml/beat, $p = 0.002$) and effective regurgitant orifice (ERO) (adjusted HR 1.52 [95% CI 1.19 to 1.91] per 10 mm^2, $p = 0.002$), which superseded traditional AR grading. Patients with QASE-severe AR (RVol $\geq$60 ml/beat or ERO $\geq$30 mm^2) versus QASE-mild AR (RVol $<$30 ml and ERO $<$10 mm^2) had lower survival (10 years: 69 $\pm$ 9% vs. 92 $\pm$ 4%, $p = 0.05$) independently of all clinical characteristics (adjusted HR 4.1 [95% CI 1.4 to 14.1], $p = 0.01$) and lower survival free of surgery for AR (10 years: 20 $\pm$ 5% vs. 92 $\pm$ 4%, $p < 0.001$, adjusted HR 12.9 [95% CI 5.4 to 38.5]). Cardiac events were considerably more frequent with QASE-severe versus -moderate or -mild AR (10 years: 63 $\pm$ 8% vs. 34 $\pm$ 6% and 21 $\pm$ 8%, $p < 0.0001$). Independent determinants of cardiac events were quantitative AR grading (QASE-severe adjusted HR 5.2 [95% CI 2.2 to 14.8], $p < 0.001$; QASE-moderate adjusted HR 2.4 [95% CI 1.06 to 6.6], $p = 0.035$), which superseded traditional AR assessment ($p < 0.001$) and LV end-systolic volume index (ESVI) (adjusted HR 1.09 [95% CI 1.03 to 1.14 per 10 ml/m^2], $p = 0.002$), which superseded LV M-mode diameters. In QASE-severe AR, patients with ESVI $\geq$45 versus $<$45 ml/m^2 had higher cardiac event rates (10 years: 87 $\pm$ 8% vs. 40 $\pm$ 10%, $p < 0.001$). Cardiac surgery for AR reduced cardiac events in patients with QASE-severe AR (adjusted HR 0.23 [95% CI 0.09 to 0.57], $p = 0.002$).

CONCLUSIONS Echocardiographic quantitation of AR severity and ESVI provides independent and superior predictors of clinical outcome in asymptomatic patients with AR and ejection fraction $\geq$50% and should be widely clinically applied. Patients with QASE-severe AR and ESVI $\geq$45 ml/m^2 should be carefully considered for cardiac surgery, which reduces cardiac events risk. (J Am Coll Cardiol Img 2008;1:1–11) © 2008 by the American College of Cardiology Foundation

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In patients with aortic regurgitation (AR), symptoms of heart failure (1–3) and reduced ejection fraction (EF) (3–5) are major determinants of outcome definitely indicating aortic valve replacement (6). However, in asymptomatic patients with preserved EF, predictors of survival after diagnosis are uncertain (7–9). These uncertainties stem from low mortality rates in young and healthy populations enrolled in natural history studies (7–9), contrasting with those observed in clinical practice (3), or from lack of a specific measure of AR severity (10). Hence, high-risk groups among asymptomatic patients with AR and left ventricular (LV) EF ≥50% are poorly defined, so that surgical indications remain unclear and are rarely applicable on the basis of current clinical guidelines (6).

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However, recent guidelines endorsed by American and European cardiology societies noted limitations of standard qualitative AR assessment (11,12) and LV assessment by diameters (13,14) and emphasized importance of quantitative measurements. These guidelines provided quantitative American Society of Echocardiography (QASE) thresholds for AR grading (10) and recommended LV volume quantitation (15) for improved LV assessment (16,17). However, the role of quantitative echocardiographic measurements in predicting outcome of asymptomatic patients with AR is unknown.

For this purpose, we prospectively enrolled asymptomatic patients with AR and EF ≥50% in whom we quantified AR and LV volumes at diagnosis with Doppler echocardiography to analyze outcome according to quantitative AR grading. We hypothesized that quantitative echocardiographic measurements (specifically QASE AR grading) independently predict clinical outcome and define high-risk patient subsets.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

EF = ejection fraction

ERO = effective regurgitant orifice

ESVI = end-systolic volume index

LV = left ventricle/ventricular

QASE = quantitative American Society of Echocardiography

RVol = regurgitant volume

METHODS

Study design. The study design was approved by institutional review board to: 1) prospectively enroll patients with AR in whom the authors quantified regurgitation and LV volumes at diagnosis; 2) have patients forming this cohort clinically managed by their independent physicians (with all information available); 3) complete all off-line echocardiographic measurements in a secure database; and then 4) record all deaths, cardiac events, and aortic valve surgeries during follow-up by their independent physicians. This design was chosen to minimize investigators' interference with patients' management, limit healthy participant bias by not requiring mandatory follow-up appointments (3,7), and ensure baseline data completion before clinical events' ascertainment. The study was designed in 1990 to 1991 (18), enrolled the first patient in 1991, and was continued with consecutive enrollment of all eligible patients examined by the authors. The American Society of Echocardiography guidelines (10), in which we (M.E.S) participated actively, were prepared later, but are in complete agreement with the present study's approaches.

Study population. After oral consent, patients were consecutively and prospectively enrolled by investigators between 1991 and 2003 if they were asymptomatic and their AR was: 1) at least mild by standard color-flow imaging (19); 2) pure (no stenosis) and isolated (no other valve disease); and 3) evaluated with quantitative echocardiography for AR degree and LV volumes. Exclusion criteria were: 1) symptoms at diagnosis (7); 2) aortic dissection or ongoing endocarditis; 3) functional AR due to hypertension; 4) associated aortic systolic gradient ≥20 mm Hg; 5) concomitant mitral valve, congenital (other than bicuspid valve), or pericardial disease; 6) previous valve repair or replacement; and 7) EF <50% (6,20). No exclusions were based on gender, age, cardiac rhythm, or treatment received.

Clinical evaluation and management. Patients were evaluated and treated by their independent physicians, who were provided with all results of Doppler echocardiography. Diagnosis of congestive heart failure was based on Framingham criteria (21). Atrial fibrillation was diagnosed by electrocardiogram. Comorbid conditions were evaluated with validated Charlson index (22). Follow-up was collected in 2006 and 2007 after closure of enrollment and of all baseline data collection procedures. Causes of events and deaths were established by review of medical, coroner, and autopsy records or death certificates.

Doppler echocardiography. AR ASSESSMENT. Comprehensive Doppler echocardiography was performed (23). The AR was prospectively assessed quantitatively and qualitatively. The AR quantitation used 3 validated methods, eventually averaged to calculate both regurgitant volume (RVol) and effective regurgitant orifice (ERO) area (85% of patients had ≥2 of 3 methods of quantification). These methods were quantitative Doppler based on aortic and mitral stroke volume measurement (18,24), quantitative 2-dimensional echocardiography on the basis of LV and mitral stroke volume (15,24), and proximal isovelocity surface area method analyzing proximal flow convergence (25). The QASE guidelines regarding AR grading (10) define regurgitant volume <30 and ≥60 ml/beat and ERO <10 and ≥30 mm^2 as thresholds for, respectively, mild and severe regurgitation. Thus, QASE-severe AR was defined as regurgitant volume ≥60 ml/beat or ERO ≥30 mm^2, QASE-mild AR required both regurgitant volume <30 ml/beat and ERO <10 mm^2, and QASE-moderate AR was larger than mild (regurgitant volume ≥30 ml/beat or ERO ≥10mm^2), but not reaching QASE-severe criteria. The AR qualitative assessment also prospectively graded AR in 4 grades and measured jet-width to LV outflow tract-width ratio (19) by color flow imaging measured from parasternal long-axis views (10).

LV ASSESSMENT. The LV end-diastolic and end-systolic volume indexes (ESVIs) and EF with Simpson disk method and LV mass were measured as recommended by the American Society of Echocardiography (15). The LV diameters by M-mode echocardiography were measured as absolute values and normalized to body surface area.

Statistical analysis. Data are presented as mean ± SD or percent. Group comparisons used analysis of variance or the chi-square test, as appropriate. The outcome end points were survival, survival free of AR surgery, and cardiac events (defined as cardiac death, congestive heart failure, or new episode of atrial fibrillation) under medical management. The entire follow-up after diagnosis under medical and surgical management was used to assess the impact of surgery on outcome with a time-dependent term in Cox proportional hazard models. Event rates with Kaplan-Meier method were expressed as estimated ± SE and compared with the log-rank test, and linearized rates of first events were estimated. Time to events was analyzed by Cox proportional hazard with calculation of unadjusted and adjusted risk ratios. Adjustment in multivariable models used age, gender, comorbidity score, and EF in models not using ESVI. Comparisons of outcome predictors (quantitative vs. traditional) used the concordance index (26); $p < 0.05$ was significant.

RESULTS

Baseline characteristics. The 251 patients enrolled in the cohort were followed for a total of 8.0 ± 3.8 years (>5 years in 188 patients, and >10 years in 82 patients; complete up to death or 2006 in 97%). All had organic aortic valve disease—due to degenerative disease (with valve thickening, annular enlargement, and central defect) in 140 patients, bicuspid valve in 60 patients, dystrophic disease (with thin leaflet, annular enlargement, with or without valve prolapse) in 19 patients, rheumatic disease in 6 patients, chronic endocarditic lesions in 6 patients, and miscellaneous causes in 20 patients. Baseline characteristics are presented in Table 1. Regurgitant volume and orifice widely ranged from 7 to 212 ml/beat and from 3 to 100 mm^2, respectively. Groups displayed by QASE grade (10) in Table 1 involve 18% QASE-mild, 43% QASE-moderate, and 37% QASE-severe. As usually noted (7,9,27), severe AR showed male predominance, a trend for younger age, lower diastolic blood pressure, and larger LV volume and mass. Jet-width ratio grading was mild (<25%) in 18%, moderate (25% to 64%) in 74%, and severe (≥65%) in 8% of patients. Vasodilator therapy ≥6 months during medical follow-up included angiotensin-converting enzyme inhibitors in 100, calcium-channel blockers in 51, and angiotensin-receptor blockers in 31 patients.

Survival and cardiac surgery after diagnosis. During follow-up, 33 deaths occurred under conservative management with survival 93 ± 2% at 5 years and 78 ± 4% at 10 years. Cardiac surgery was performed in 81 patients: 1 for aortic dissection and 80 for AR. Indications for surgery for AR were occurrence of symptoms in 38, LV dysfunction or enlargement in 17, aortic aneurysm in 11, infective endocarditis in 3, and physician and/or patient preference in 11 patients. The 10-year rate of surgery for AR was 36 ± 4%. Thus, for the combined end point of survival and freedom from surgery for AR, 113 events (33 deaths, 80 surgeries) occurred with a rate of 50 ± 4% at 10 years.

Univariately (or after adjustment) qualitative assessment of AR in 4 grades, with jet-width ratio as a continuous or categorical variable, showed no significant association to survival (all $p > 0.15$). Conversely, quantitative AR measurements were associated with survival after diagnosis univariately (RVol adjusted hazard ratio [HR] 1.17 [95% confidence interval (CI) 1.05 to 1.30]/10 ml, $p < 0.01$; ERO adjusted HR 1.50 [95% CI 1.16 to 1.86]/10 mm^2, $p < 0.01$) and in multivariable analysis as continuous variables or as QASE-severe AR grading (adjusted HR 4.1 [95% CI 1.4 to 14.1] compared with QASE-mild AR, $p = 0.01$) (Table 2). Stratified by QASE-AR grading, survival under

Table 1. Baseline Characteristics of Asymptomatic Patients According to Quantitative AR Grading

AR Quantitative Classification	Overall (n = 251)	QASE-Mild* (n = 51)	QASE-Moderate* (n = 107)	QASE-Severe* (n = 93)	p Value
Clinical characteristics					
Age, yrs	60 ± 17	62 ± 15	62 ± 18	58 ± 18	0.16
Male gender, n (%)	167 (67)	22 (43)	67 (63)	78 (84)	<0.001
Atrial fibrillation, n (%)	11 (4)	1 (2)	6 (6)	4 (4)	0.58
Hypertension history, n (%)	123 (49)	30 (58)	54 (51)	39 (42)	0.20
Diabetes, n (%)	13 (5)	1 (2)	5 (5)	7 (8)	0.38
Charlson comorbidity index, arbitrary units	1.9 ± 2.4	1.3 ± 1.8	2.2 ± 2.5	1.8 ± 2.4	0.05
Systolic blood pressure, mm Hg	139 ± 22	140 ± 24	138 ± 20	140 ± 24	0.90
Diastolic blood pressure, mm Hg	71 ± 12	77 ± 14	74 ± 10	64 ± 13	<0.001
Left ventricular characteristics					
Ejection fraction, %	68 ± 9	71 ± 9	68 ± 9	67 ± 9	0.05
End-systolic diameter index, mm/m^2	18 ± 3	17 ± 3	18 ± 3	20 ± 4	<0.001
End-diastolic volume index, ml/m^2	105 ± 25	73 ± 15	95 ± 18	133 ± 35	<0.001
End-systolic volume index, ml/m^2	34 ± 16	22 ± 9	31 ± 12	45 ± 22	<0.001
Left ventricular mass, g	248 ± 76	187 ± 57	231 ± 72	300 ± 89	<0.001
AR characteristics					
Jet to outflow tract width ratio, %	39 ± 14	27 ± 12	35 ± 13	49 ± 15	<0.001
Regurgitant volume, ml/beat	55 ± 21	17 ± 5	41 ± 12	92 ± 32	<0.001
ERO, mm^2	24 ± 12	7 ± 2	18 ± 6	41 ± 18	<0.001

*Quantitative American Society of Echocardiography (QASE)-severe aortic regurgitation (AR): regurgitant volume ≥60 ml/beat or effective regurgitant orifice (ERO) ≥30 mm^2; QASE-mild AR: regurgitant volume <30 ml/beat and ERO <10 mm^2; and QASE-moderate AR: regurgitation > mild (regurgitant volume ≥30 ml/beat or ERO ≥10 mm^2) but not reaching QASE-severe criteria.

conservative management was lower in QASE-severe versus QASE-moderate and QASE-mild AR (at 5 years, 82 ± 6% vs. 95 ± 2% and 98 ± 2%, respectively, $p = 0.05$) (Fig. 1). Adjusting additionally for vasodilator therapy use, QASE-severe AR remained independently associated with higher mortality (adjusted HR 6.7 [95% CI 2.2 to 23.2], $p = 0.02$). The QASE-moderate compared with QASE-mild grading showed a trend for higher mortality (adjusted HR 2.1 [95% CI 0.8 to 6.7], $p = 0.13$). The LV end-systolic diameter (absolute or normalized to body surface area) was univariately associated with survival (both $p < 0.04$), and ESVI showed a trend of association ($p = 0.12$), but both were no longer significant after adjustment for quantitative AR assessment (all $p > 0.30$).

In QASE-severe versus QASE-moderate and QASE-mild AR, surgery for AR was more often performed (at 10 years, 72 ± 6% vs. 24 ± 5% and vs. 0%, respectively, $p < 0.0001$), so that the rate of survival free of surgery for AR was lower in QASE-severe AR (at 10 years, 20 ± 5% vs. 57 ± 6% and 92 ± 4%, respectively, $p < 0.0001$; adjusted risk ratio 12.9 [95% CI 5.4 to 38.5] for QASE-severe AR and 4.0 [95% CI 1.7 to 11.8] for QASE-

Table 2. Association of Survival Free of Surgery for AR and of Cardiac Events With Quantified Degree of AR and ESVI

		Outcome Under Medical Management					
		Survival* (n = 33)		Survival Free of AVR† (n = 113)		Cardiac Events† (n = 67)	
	Threshold	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value
QASE-severe AR‡	Compared with QASE-mild‡	4.1 (1.4–14.1)	0.01	12.9 (5.4–38.5)	<0.001	5.2 (2.2–14.8)	<0.001
RVol	Per 10-ml/beat increment	1.22 (1.08–1.35)	0.002	1.22 (1.16–1.28)	<0.001	1.11 (1.05–1.17)	<0.001
ERO	Per 10-mm^2 increment	1.52 (1.19–1.91)	0.002	1.42 (1.28–1.57)	<0.001	1.17 (1.04–1.30)	0.01
ESVI ≥45 ml/m^2	Compared with <45 ml/m^2	—	—	1.8 (1.2–2.7)	0.01	2.4 (1.3–4.3)	0.005

Cardiac events: cardiac death, congestive heart failure, or new episode of atrial fibrillation. *Hazard ratios are presented with their 95% confidence intervals in parentheses and were adjusted for age, gender, AR quantitative classification, ejection fraction, and comorbidity index. †Hazard ratios are presented with their 95% confidence interval in parentheses and were adjusted for age, gender, AR quantitative classification, end-systolic volume index (ESVI), and comorbidity index. ‡QASE-severe AR: regurgitant volume (RVol) ≥30 ml/beat or ERO ≥20 mm^2; QASE-mild AR: RVol <30 ml/beat and ERO <10 mm^2.
Abbreviations as in Table 1.

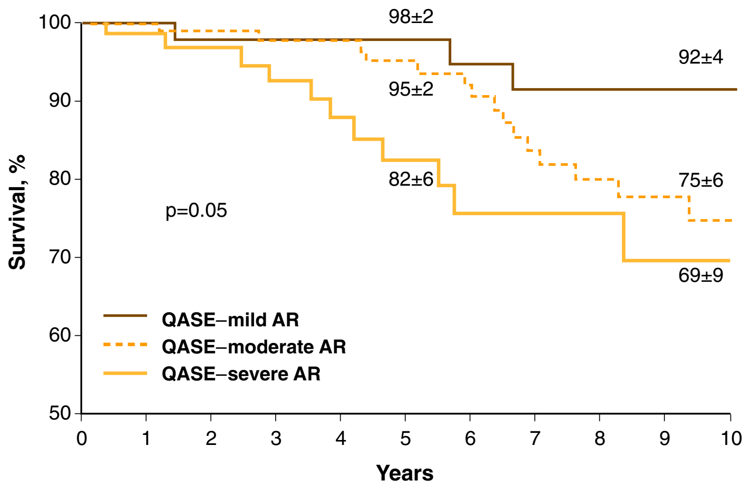

Figure 1. Survival Under Conservative Management After Diagnosis of Asymptomatic Aortic Regurgitation

Patients are stratified according to quantitative American Society of Echocardiography (QASE) aortic regurgitation (AR) grading. The QASE-severe AR is defined as regurgitant volume ≥60 ml/beat or effective regurgitant orifice (ERO) ≥30 mm^2 **(yellow line)**, QASE-mild AR as regurgitant volume <30 ml/beat and ERO <10 mm^2 **(brown line)**, and QASE-moderate AR **(dotted orange line)** as larger than mild (regurgitant volume ≥30 ml/beat or ERO ≥10 mm^2), but not reaching QASE-severe criteria. The 5- and 10-year survival rates ± SE are indicated. Note the lower survival with QASE-severe AR, whereas QASE-moderate AR displays survival similar to QASE-mild AR up to 5 years after diagnosis, with higher mortality thereafter.

moderate AR vs. QASE-mild AR, both $p < 0.001$) (Fig. 2, Table 2). In patients with QASE-severe AR, linearized yearly mortality rates were markedly lower after AR surgery (1.7% [95% CI 0.8 to 3.1]) than under conservative management (3.4% [95% CI 1.9 to 5.6]), but the time-dependent mortality reduction did not reach statistical significance (risk ratio 0.64, $p = 0.38$).

Cardiac events. Under conservative management, 67 patients incurred cardiac events (cardiac death, congestive heart failure, or new atrial fibrillation) with 5- and 10-year rates of 27 ± 3% and 39 ± 4%,

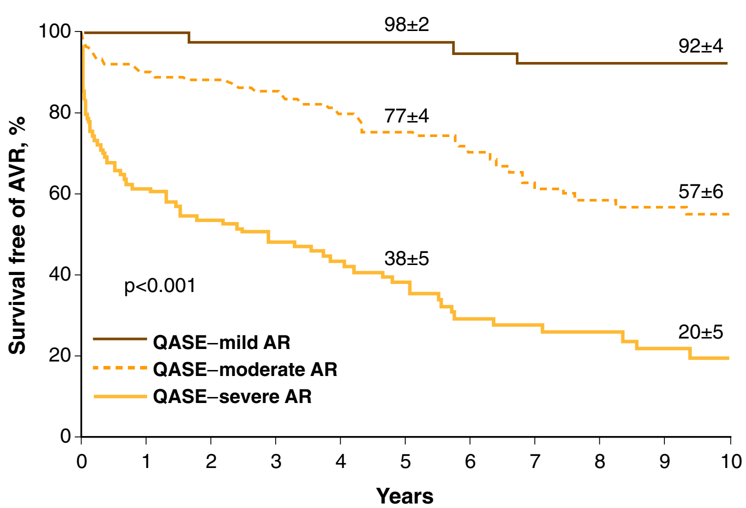

Figure 2. Composite End Point of Survival Free of Surgery for AR After Diagnosis of Asymptomatic AR

Patients are stratified according to QASE AR grading. The QASE-severe AR is defined as regurgitant volume ≥60 ml/beat or ERO ≥30 mm^2 **(yellow line).** The QASE-mild AR as regurgitant volume <30 ml/beat and ERO <10 mm^2 **(brown line)**, and QASE-moderate AR **(dotted orange line)** as larger than mild (regurgitant volume ≥30 ml/beat or ERO ≥10 mm^2), but not reaching QASE-severe criteria. The 5- and 10-year rates of the end point ± SE are indicated. Note the wide difference in outcome according to QASE grading at baseline. AVR = aortic valve replacement; other abbreviations as in Figure 1.

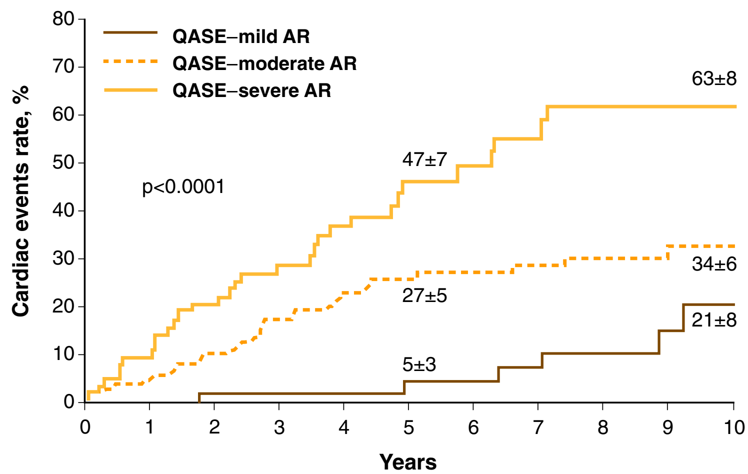

Figure 3. Cardiac Events (Cardiac Death, Congestive Heart Failure, and New Atrial Fibrillation) Under Conservative Management After Diagnosis of Asymptomatic AR

Patients are stratified according to QASE AR grading. The QASE-severe AR is defined as regurgitant volume ≥60 ml/beat or ERO ≥30 mm² **(yellow line)**, QASE-mild AR as regurgitant volume <30 ml/beat and ERO <10 mm² **(brown line)**, and QASE-moderate AR **(dotted orange line)** as larger than mild (regurgitant volume ≥30 ml/beat or ERO ≥10 mm²), but not reaching QASE-severe criteria. The 5- and 10-year event rates ± SE are indicated. Note the progressive increase in event rates with the severity of QASE-grading of AR. Abbreviations as in Figure 1.

respectively. All measures of AR severity, traditional (qualitative 4-grade classification, jet-width ratio continuous or categorical) or quantitative (RVol, ERO), were univariately predictive of cardiac events (all $p < 0.01$). However, in models with quantitative AR grading, traditional AR assessments were no longer significant in predicting cardiac events (all $p > 0.23$). Comparison of outcome prediction involving traditional AR assessment demonstrated superiority of QASE-grading for predicting cardiac events (all $p < 0.001$). The RVol and ERO remained predictive of cardiac events after adjustment in multivariable analysis (Table 2). Stratified by QASE grading, cardiac event rates were considerably different (Fig. 3). In multivariable analysis (Table 2) adjusted for age, gender, comorbidity index, and LV ESVI, QASE-severe AR (adjusted risk ratio 5.2 [95% CI 2.2 to 14.8] $p < 0.001$ vs. QASE-mid AR) and QASE-moderate AR (adjusted risk ratio 2.4 [95% CI 1.06 to 6.6], $p = 0.035$ vs. QASE-mild AR) were independently predictive of cardiac events, even after adjusting for vasodilator use.

All measures of LV end-systolic enlargement, traditional (LV diameter absolute or body surface area normalized) or volumetric (ESVI), were univariately predictive of cardiac events (all $p < 0.01$). However, in models with ESVI, traditional measures lost significance in predicting cardiac events (both $p > 0.09$). Comparison of outcome prediction involving LV end-systolic diameter (absolute or body surface area normalized) demonstrated superiority of ESVI for predicting cardiac events (both $p < 0.002$). Baseline ESVI was predictive of cardiac events univariately (adjusted HR 1.09 [95% CI 1.03 to 1.14]/10 ml/m², $p = 0.002$) and in multivariable analysis (adjusted HR 1.23 [95% CI 1.03 to 1.46]/10 ml/m² or 2.4 [95% CI 1.3 to 4.3] for ESVI ≥45 ml/m²) (Table 2). Stratified by ESVI categories (<45, ≥45 ml/m²), 10-year cardiac event rates were considerably different overall (31 ± 5% vs. 74 ± 8%, $p < 0.001$) with progressively increasing rates in combination with stratification using QASE AR grading (Fig. 4).

Ten-year rates of atrial fibrillation were 14 ± 7%, 14 ± 4%, and 19 ± 7% in QASE-mild, QASE-moderate, and QASE-severe AR, respectively ($p = 0.02$). If patients with atrial fibrillation as the only cardiac event are excluded, 61 patients had cardiac events (cardiac death or heart failure), with 10-year rates of 18 ± 8%, 29 ± 5%, and 65 ± 8% in QASE-mild, QASE-moderate, and QASE-severe AR, respectively ($p < 0.001$). These events were predicted independently by QASE-severe AR (adjusted HR 5.9 [95% CI 2.3 to 18.3], $p < 0.001$) and ESVI ≥45 ml/m² (adjusted HR 2.2 [95% CI 1.2 to 3.9], $p = 0.01$), with borderline effect of QASE-moderate AR (adjusted HR 2.3 [95% CI 0.95 to 7.0], $p = 0.065$). Of note, ESVI ≥45 ml/m² is similarly predictive of atrial fibrillation (adjusted HR 2.9 [95% CI 1.6 to 5.1], $p = 0.02$) and heart failure (adjusted HR 3.4 [95% CI 1.2 to 9.2], $p < 0.001$).

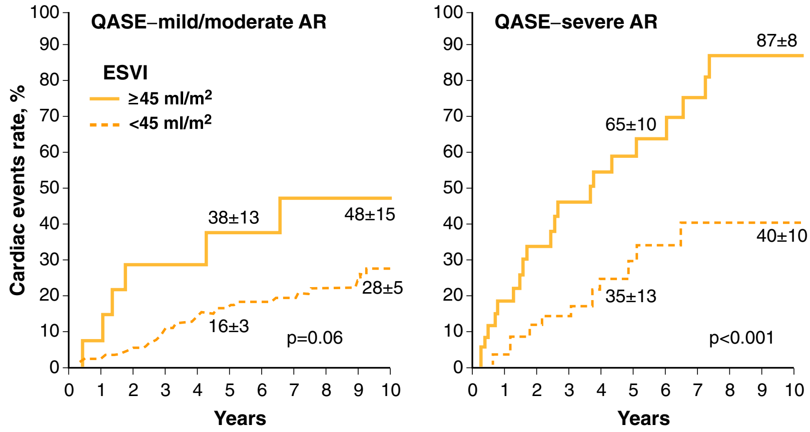

Figure 4. Impact of ESVI Level on Cardiac Event Rates After Diagnosis of Asymptomatic AR

Cardiac events (cardiac death, congestive heart failure, and new atrial fibrillation) under conservative management after diagnosis of asymptomatic AR according to the left ventricular end-systolic volume index (ESVI, <45 ml/m^2 **[dotted line]** or ≥45 ml/m^2 **[solid line]**) stratified by quantitative AR grading. The **left graph** indicates cardiac events in patients with QASE-mild or QASE-moderate AR grades. The **right graph** indicates rates in QASE-severe AR grade. Note the higher cardiac events rates (indicated at 5 and 10 years ± SE) with ESVI ≥45 ml/m^2, particularly with QASE-severe AR. Abbreviations as in Figure 1.

The effect of age on outcome was analyzed by stratifying patients age <50 and ≥50 years at diagnosis (Fig. 5). Whereas mortality was minimal below age 50 years irrespective of AR severity, QASE grading was predictive of mortality after age 50 years (Figs. 5A and 5C). Only 9 patients incurred myocardial infarction during follow-up and none died, so that the age–mortality link is unlikely to be related to coronary disease. Notably, QASE-severe AR was similarly predictive ($p = 0.84$) of a high risk of cardiac events irrespective of age (Figs. 5B and 5D).

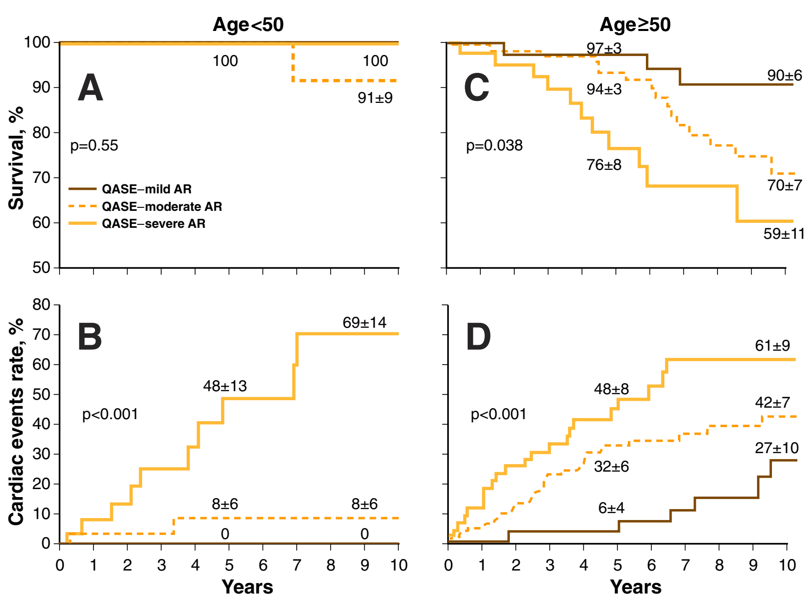

Figure 5. Effect of Age (<50 and ≥50 Years) on Survival After Diagnosis and Cardiac Events

In each **panel,** survival or event rates are indicated at 5 and 10 years ± SE. Note the low mortality in patients age <50 years (**A**, 10-year survival 100%, 91 ± 9%, and 100% in QASE-mild, QASE-moderate, and QASE-severe, respectively), whereas mortality is higher after age 50 years **(C)** and significantly related to QASE-grading of AR. Cardiac events are significantly different according to QASE grading in patients age <50 **(B)** and ≥50 years **(D)** and are similar irrespective of age with QASE-severe AR ($p = 0.84$). Abbreviations as in Figure 1.

With the entire follow-up in models with time-dependent surgery for AR, patients with QASE-moderate AR showed no significant reduction of cardiac events after surgery ($p = 0.92$). Conversely, for QASE-severe AR, surgery for AR was associated with marked reduction of cardiac events (linearized yearly rates 11.2% [95% CI 7.9 to 15.3] under medical management decreasing to 2.3% [95% CI 0.9 to 5.0] after surgery, adjusted risk ratio 0.23 [95% CI 0.09 to 0.57], $p = 0.002$). Also in patients with ESVI $\geq$45 ml/m^2, surgery for AR was associated with marked reduction of cardiac events (linearized yearly rates 14.9% [95% CI 10.2 to 21.0] under medical management decreasing to 2.9% [95% CI 1.3 to 6.0] after surgery, adjusted risk ratio 0.22 [95% CI 0.08 to 0.62], $p = 0.004$). If patients with atrial fibrillation as the only cardiac event are excluded, surgery for AR markedly lowered the event rate (0.16 [95% CI 0.05 to 0.47], $p < 0.01$).

DISCUSSION

The present prospective cohort demonstrates the impact of quantitative echocardiography on the clinical outcome of asymptomatic patients with AR and EF $\geq$50%. The RVol and ERO are powerful independent predictors of outcome, and patients with QASE-severe AR (RVol $\geq$60 ml/beat or ERO $\geq$30 mm^2) incur excess mortality, cardiac events, and lower survival free of surgery for AR. Additionally, baseline ESVI $\geq$45 ml/m^2 independently predicts cardiac events. These quantitative measures supersede predictive power of traditional variables (jet assessment and LV diameters), underscoring their importance to clinical decisions. Patients at high risk of cardiac events display a marked reduction of risk after cardiac surgery for AR (risk almost 5 times lower) so that surgery should be considered in patients with QASE-severe AR and ESVI $\geq$45 ml/m^2.

Rationale of the study. Patients with AR and symptoms or reduced ventricular function are at higher risk of cardiovascular death (6). In previous smaller prospective studies (7–9), defining high-risk subsets among asymptomatic patients with preserved LVEF was challenging. Indeed, these series observed only a few deaths (average mortality 0.4%/year) (7–9), contrasting with clinical practice in which patients are older (closer to 60) and mortality of asymptomatic patients with AR is higher (2.8%/year) (3), close to our present series. Thus, clinical guidelines are based on data involving low mortality and cardiac events and on inconsistent LV markers of clinical outcome (6). Recommendation of LV diameters, particularly end-systolic diameter $\geq$55 mm, for class II indications of surgery is poorly substantiated (6). In our study, only 3 (1.2%) had such diameters and 95% had both LV end-diastolic diameter <70 mm and end-systolic diameter <50 mm, which represents a contraindication (class III indication) for surgery by clinical guidelines (6). Conversely, 44 (17.5%) of our patients had both QASE-severe AR and ESVI $\geq$45 ml/m^2 and were at high risk. Therefore, traditional LV indexes used in AR are quite insensitive. Emerging clinical tools by quantitative echocardiography, measuring absolute AR-degree (RVol or ERO) and total LV consequences of AR (LV volumes) raised new hopes. These tools were developed in physiologic studies (18,24,28), codified by guidelines of the American Society of Echocardiography (10,15), and endorsed by major American and European cardiac societies, but their impact on clinical outcome was unknown. In view of insensitivity and prognostic inferiority of traditional tools (LV diameters) for detecting high-risk patients (6), the present data are essential in managing asymptomatic patients with AR and preserved EF, among which high-risk subsets can now be identified and aggressively managed.

Quantitation of AR. The link between AR degree and outcome might seem intuitive, but reports of "severe" AR with very low mortality (7,8,29) cast doubts on such a link, which was never analyzed, probably because traditional AR assessment has serious limitations (11,12). Quantitative methods (10) provided encouraging risk stratification in other valve regurgitations (30). Ancillary questions regarding potential superiority of quantitative assessment and specific thresholds proposed by QASE grading (18,24) required outcome data. The present study fills these gaps of knowledge and shows that QASE AR grading strongly predicts outcome in asymptomatic patients with EF $\geq$50%, is more sensitive, and supersedes traditional measures of AR severity, providing essential support for quantitative assessment. A QASE-severe AR defines patients at notable risk of mortality, cardiac events, and with lower survival free of surgery for AR, genuinely justifying the severe label. Hence, for patients in whom surgery is not indicated by clinical guidelines (6), quantitative echocardiography identifies those at high risk of poor outcome under medical management and improved outcome with surgery and is particularly important and relevant.

We averaged 3 methods of AR quantitation for simplicity of presentation. Methods correlate with r $\geq$ 0.90, and all predict cardiac events similarly, so that in clinical practice measuring all methods is not always indispensable to optimize feasibility. In mitral regurgitation, ERO carries the most predictive power (30), but in AR, ERO measuring lesion severity and RVol measuring volume overload (24) are equipotent for outcome prediction and complementary.

Quantitation of LV volumes. Patients with LV dysfunction complicating AR incur high mortality (3), even after surgery (5). However, in patients with "normal" EF, LV dysfunction development is rare (7,29). Disagreement on ventricular indexes predicting outcome (3,7,8,29) reflects LV diameter's shortcomings as a measure of LV remodeling (13). The ESVI was assessed in a small angiographic series examining only post-operative outcome (16,17). Our study provides new information with echocardiographic ESVI predicting clinical outcome and superseding LV diameters. Despite "preserved" EF, higher ESVI ($\geq$45 ml/m^2) independently predicts more cardiac events within each AR grade. This result reconciles previous discordant data (3,7,16,17,29,31,32) and, by normalizing to body size, is equally applicable to men and women, avoiding gender-bias from non-normalized LV dimensions (14). Thus, quantitative echocardiography provides comprehensive determinants of outcome and is essential for clinical management of asymptomatic AR.

Clinical implications. Quantitative echocardiography defines prognosis in patients with AR and should be encouraged and generalized (10,15). The RVol and ERO should be measured at diagnosis; patients reaching thresholds ($\geq$60 ml/beat, $\geq$30 mm^2, respectively) have severe AR and, with ESVI $\geq$45 ml/m^2, are at risk for poor outcome. Considerable post-operative outcome improvement is a strong incentive to consider surgery. Patients with either (but not both) quantitative criteria (QASE-severe AR or ESVI $\geq$45 ml/m^2) should be carefully monitored for progression of AR or LV remodeling (33).

Patients $<$50 years incur minimal mortality. Thus, studies enrolling mostly young patients observed few deaths, and their suggestion that symptom-based decision-making is sufficient in AR (34) might be biased. In our series, cardiac events were similarly frequent with QASE-severe AR in young and older patients. Thus, QASE-severe AR and ESVI $\geq$45 ml/m^2 should lead, even in younger patients, to consideration of surgery.

Study limitations. Our study was restricted to patients with preserved EF. Lack of association of EF with outcome does not obviate prompt surgical consideration in patients with low EF who are at high risk (3,5,6,20). The link between AR and atrial fibrillation might be disputed, but our data show that after exclusion of patients with atrial fibrillation as the only cardiac event, our results are unaffected and AR quantitative grading and ESVI predict outcome. In comparing outcome implications of quantitative and jet-based data, it is important to account for jet direction and AR etiology. However, jet-width ratios were not different when stratified by QASE-grading according to jet eccentricity (all $p > 0.31$) or AR etiology (all $p > 0.17$). For prediction of outcome, jet-width ratio impact was not improved by focusing on central jets, and individual variables such as pressure half-time or aortic arch were not independently predictive of outcome (all $p > 0.11$), confirming the superior outcome predictive power of quantitative versus qualitative AR grading.

Loss of follow-up might bias the estimation of outcome but was minimal in our study. Series analyzing outcome with data mining risk overfitting (35). Examining few prospectively predefined variables obviates overfitting, which is unlikely here.

Vasodilator treatment of AR is disputed (36,37) and inconsistently used, and we cannot draw conclusions regarding subsets in which vasodilators might be beneficial.

CONCLUSIONS

The present prospective study shows that quantitative echocardiography provides independent and superior predictors of clinical outcome in AR and should be routinely performed. Asymptomatic patients with EF $\geq$50% but QASE-severe AR (RVol $\geq$60 ml/beat or ERO $\geq$30 mm^2) and ESVI $\geq$45 ml/m^2 are at a high risk of mortality and cardiac events. Cardiac surgery for AR, which markedly reduces this risk, should be carefully clinically considered.

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